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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
GUCKER, STEPHEN	
ART UNIT	**PAPER NUMBER**
1649	

DATE MAILED: 10/16/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/063,569	GODDARD ET AL.	
	Examiner	Art Unit	
	Stephen Gucker	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6-8 and 11-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6-8 and 11-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/24/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Response to Amendment

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/24/06 has been entered.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Any objections or rejections made in a previous Office Action that are not herein reinstated have been withdrawn.

4. Claims 6-8 and 11-17 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility for reasons of record and the following. The instant application puts forth the assertion that the claimed polypeptides are useful for the diagnosis and treatment of disease states. The disclosure proposes that the diagnosis of disease states by the claimed polypeptides can occur through detection of the PRO3566 proteins in biological samples by various binding assays, for example, by using labeled antibodies. The specification also discloses that the claimed polypeptides could be used to screen for agonist or antagonist compounds (small organic molecules or other peptides/proteins) that either potentiate or inhibit the activity of the PRO3566 proteins. The specification argues that the claimed polypeptides could be used as

pharmaceuticals directly or that variants or fragments of the claimed polypeptides could be used as pharmaceuticals. Antibodies and modified antibodies (chimeric antibodies, humanized antibodies, covalently-linked antibodies, immunoconjugates, etc.) to the PRO3566 proteins could be used to bind to the proteins and either potentiate or inhibit the activity levels of the proteins. The instant application also teaches that antibodies that bind to the PRO3566 proteins could be used to isolate or purify the PRO3566 proteins.

Upon searching and examination, it is the Examiner's position that the claimed genus of proteins, based SEQ ID NO:64 (the amino acid sequence of the polypeptide, otherwise known as PRO3566), do not have a well-established utility known in the prior art because the application has not identified any well-established utility that is particular to PRO3566, and the Examiner has not found any such utility in the prior art of record. Furthermore, the instant disclosure does not provide a specific utility for that which is claimed for the following reasons. Applicant asserts that PRO3566 proteins could be used as molecular weight markers for protein electrophoresis. This would be true for all all proteins of the same molecular weight as the PRO3566 protein, and this is not a specific utility. Applicant asserts that antibody detection of the PRO3566 sequences could be used for tissue typing, but Applicant provides no teachings that PRO3566 is limited to any particular type of tissue. It is also noted that every tissue type of the body produces its own specific markers, so again, this asserted utility is not specific.

The instant disclosure is silent as to the actual biological activity or function of PRO3566. Without some minimal teaching as to the amount or level of activity of

PRO3566 protein in either a normal or disease state, the artisan is without guidance or direction as to what any change in amount or level of activity of PRO3566 would indicate and what therapeutic course of action should follow. For example, it is completely unknown as to what a rise in the level or activity of PRO3566 proteins would indicate in a cancerous tissue. Would a rise in PRO3566 indicate that an increased level or activity associated with cancer meant that the activity or function of the PRO3566 proteins needed to be suppressed, under the assumption that PRO3566 was somehow causative or contributory to the pathology of cancer? Or would a rise in PRO3566 indicate that the tissue was attempting to combat the cancer by turning on or activating cancer suppressing genes? (An example known in the art of a cancer suppressing gene is p53). In which case, the artisan would desire to further increase the activity or level of PRO3566 and not suppress or inhibit it. Because the instant application does not provide some minimal context as to what altered levels of PRO3566 protein means, either up or down, the artisan can find no diagnostic or therapeutic utility for the claimed polypeptides because significant and substantial further research would need to be performed in order to answer these simple but vital questions. This is especially true with the instant invention because PRO3566 mRNA is asserted by Applicant to be expressed at a *higher* level in esophageal tumor *but at a lower* level in melanoma, as compared to normal esophagus and skin tissue. It is clear that substantial further research would need to be performed to place this finding into a meaningful real world context for the encoded protein and specific antibodies to such, because without further experimentation, it cannot be determined from the encoding mRNA level if the protein

level is changing in any correlated fashion with the mRNA level. Without an answer to these vital questions, not only do the PRO3566 proteins have no substantial therapeutic utility, but the antibodies to the protein have no substantial therapeutic utility as well because no meaningful therapeutic administration of the PRO3566 proteins or antibodies can be accomplished without the minimal knowledge of whether increased or decreased levels or activities of PRO3566 mRNA indicates a change in protein level, and in regards to a therapeutic utility, whether a change in protein level is a deleterious or beneficial biological event.

In regards to the asserted utilities of using the PRO3566 proteins and the antibodies to the proteins for screening assays to find drugs or endogenous ligands, receptors, or other compounds that interact with or bind to PRO3566, without some minimal knowledge as to the function or significance of PRO3566 in a biological context, said asserted utilities are not substantial because significant further research would have to be performed in order to know why or for what purpose the artisan would want to activate or inhibit the biological function of PRO3566 in the first place. In other words, without at least some knowledge as to the function or activity of PRO3566 in either normal or diseased tissue (the disclosure is silent to both), the artisan has no substantial utility for any of the substances that interact with PRO3566 in an assay until substantial further research is conducted that reveals the biological utility of PRO3566 itself.

In regards to the asserted diagnostic utility of detecting PRO3566 proteins with the antibodies, the same reasoning that applied to the lack of substantial

therapeutic utility would also apply to a showing of a lack of substantial diagnostic utility. Without a minimal knowledge as to what an appropriate level or activity of the PRO3566 proteins are in healthy normal appropriate control tissue and how they would differ in pathological tissue afflicted with specific diseases, the finding of the absence or presence of PRO3566 proteins in tissue with antibodies does not provide artisans with any workable information they could act on in a diagnostic fashion because the instant disclosure does not present a persuasive case that PRO3566 polypeptide sequences are significantly altered in any way in any pathology. The only teaching offered by the specification indicates that PRO3566 nucleic acid is differentially expressed in melanoma and esophageal tumor sample as compared to normal tissue, but there is no teaching as to the magnitude or statistical significance of the differential expression by which a reasonable determination could be made that the protein levels correlated with the mRNA levels. No data or statistical information is provided by the specification as to how the determination of overexpression was made in the tumor samples. Was the differential expression statistically significant or just the result of chance? How large was the differential expression, a little or a lot? Small changes in mRNA levels, while being accurately measurable by quantitative reverse phase polymerase chain reaction (RT-PCR), are not nearly as accurately measurable at the protein level using antibodies. Example 18 of the instant specification (PRO3566 is found on page 142 "DNA59844-2542") does not indicate any quantitative or numerical results, such that it is not clear how large any "overexpression" or "underexpression" is and whether such differences are big enough to measure at the encoded protein level. Haynes et al. (Electrophoresis

19:1862-1871, 1998), who studied more than 80 proteins relatively homogeneous in half-life and expression level, found no strong correlation between protein and transcript level. For some genes, equivalent mRNA levels translated into protein abundances which varied more than 50-fold (hence, the 2-fold difference asserted by Applicants is not particularly persuasive). Haynes et al. concluded that the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript (p. 1863, second paragraph, and Figure 1). Given the paucity of information, the data do not support the implicit conclusion of the specification that PRO3566 polypeptide shows overexpression in esophageal tumor and underexpression in normal skin, much less that the levels of PRO3566 polypeptide would be diagnostic of such by employing the PRO3566 specific antibodies. Significant further research would have been required of the skilled artisan to determine whether PRO3566 is differentially expressed in any cancer to the extent that it could be used as a cancer diagnostic, and thus the asserted utility is not substantial. The literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. Without more specifics about necessary sample size, expression level range for normal and tumor tissues, the specification has not provided the invention in a form readily usable by the skilled artisan such that significant further experimentation is unnecessary. There is absolutely no evidence of record at all regarding whether or not PRO3566 polypeptide levels are differentially expressed in tumors, which is crucial, because the PRO3566 specific antibodies react with PRO3566 polypeptide, and not with PRO3566 mRNA.

Applicants arguments filed 7/24/06 have been fully considered but they are not persuasive because Applicants argue that mRNA for the PRO3566 polypeptide is more highly expressed in normal skin compared to melanoma tumor, and in esophageal tumor compared to normal esophagus, and submit the first declaration of J. Christopher Grimaldi to support their assertion. The Examiner is persuaded by the evidence and declarations submitted by Applicants that when using quantitative RT-PCR, 2-fold differences in nucleic acid level can be meaningfully and reliably measured. In fact, the Examiner has previously examined the PRO3566 nucleic acid sequences and approved them to issue as a US patent. Where the Examiner disagrees with Applicant is that 2-fold differences in encoding nucleic acid can be usefully measured with antibodies at the protein level in order to diagnose cancer because Applicant has not demonstrated that the PRO3566 polypeptide level, and not the nucleic acid level, is appreciably different in cancer because of the teachings of the prior art that indicate that larger differences in nucleic acid levels would be required to render the claimed invention as having utility without having to resort to undue further experimentation, contrary to the second declaration of J. Christopher Grimaldi, where he states that when a gene is overexpressed 2-fold, the gene product or polypeptide will also be overexpressed. Similarly, the declaration of Dr. Paul Polakis avers that mRNA levels typically correlate with an increase in abundance of the encoded protein.

Applicant argues that the limited teachings in Chen et al. that do address changes in mRNA level show that it is more likely than not that increased mRNA expression correlates well with increased protein expression. Applicant's arguments

concerning the results in Chen have been fully considered but are not found to be persuasive. The results in Chen et al. shown in Figure 2A-2C represent three examples wherein protein levels correlated well with mRNA (out of 17 identified). However, Chen et al. also reported 137 proteins spots wherein protein levels did not correlate with mRNA levels. While Chen et al. does not report the individual variation within any of these samples (which included normal tissue and tumor tissue) and therefore may or may not have included mRNAs and/or proteins that were differentially expressed, Chen et al. clearly teaches that mRNA levels are not predictive of protein levels, stating "[t]he use of mRNA expression patterns by themselves, however, is insufficient for understanding the expression of protein products, as additional post-transcriptional mechanisms, including protein translation, post-translational modification, and degradation, may influence the level of a protein present in a given cell or tissue" (See pg 304, second column).

Applicants argue that in Nelson v. Bowler, the CCPA says that specific therapeutic use of a compound is not necessary if there are tests which evidence pharmacological activity of a compound. The argument has been fully considered, but is not persuasive. In Nelson, the court held that the compound of which utility was in question was shown to have a specific pharmacological activity measured by dispositive tests. "In other words, one skilled in the art at the time the tests were performed would have been reasonably certain that 16-phenoxy PG's had practical utility." (885). "Here, however, a correlation between test results and pharmacological activities has been established." (886) Unlike in Nelson, the instant application does not have a showing of

practical utility because the specification does not allow the skilled artisan to use the instant invention for the reasons previously discussed. It is maintained that the instant application has not established a correlation between higher expression of the PRO3566 mRNA and polypeptide or the diagnostic use of the encoded protein.

Applicant's cite Alberts et al. (Molecular Biology of the Cell, 1994 and 2002, filed 7/24/06) for showing the steps at which eukaryotic gene expression can be controlled, correlating transcription with protein. This argument has been fully considered but is not deemed persuasive. It is noted that the field of proteomics was very new in 1994, when the first cited teachings of Alberts were published. Additionally, the references of Haynes et al. and Chen et al. clearly show that one cannot reasonably expect that for any given mRNA the level of protein produced therefrom will correlate with the amount of mRNA.

Applicants also cite Lewin (Genes VI, 1997, filed 1/31/06) and Zhigang et al. (World J. Surg. Oncol, 2004, filed 1/31/06) to support the ideas of Alberts et al. (above), with the example of Zhigang et al. showing that there is a high correlation between PSCA protein and mRNA expression. This argument has been fully considered but is not deemed persuasive. Lewin teaches the same idea that Alberts et al. do. Lewin states that "having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that the overwhelming majority of regulatory events occur at the initiation of transcription." Genes V1 at 847-848 (emphasis added by Examiner). Lewin says that one cannot presume a correlation between RNA and protein, even though

most regulator events occur when DNA is transcribed. There is convincing evidence of record that in some cases transcription is the controlling factor but in others it is translation. Zhigang find that a correlation between mRNA and protein expression for the PSCA nucleic acid examined occurred in 93% of the samples so that it may be a promising diagnostic marker. There is no requirement for utility that a 100% correlation be present. Nevertheless, in the instance application we have no correlation. There is no suggestion in the specification of multiple tumors tested. There are just "cDNA libraries isolated from different human tumor and normal human tissue samples." The declaration of Grimaldi says these samples were pooled samples. No relative or absolute values of expression for protein or nucleic acid were given in the specification. As discussed above, it is not clear whether one would reasonably expect higher expression in 10/10 or 1/20 tumors tested for the PRO3566 nucleic acid and/or protein. If Zhinghan et al. had obtained only a 5% correlation, it is doubtful he would have concluded that the nucleic acid would be a promising molecular marker.

Applicant refers to the second declaration of Dr. Polakis (Polakis II), submitted with the response filed 7/24/06. Applicant argues that this declaration provides the facts, set forth in a table (Exhibit B), for independent evaluation by the Examiner. The second Polakis declaration under 37 CFR § 1.132 filed 7/24/06 is insufficient to overcome the rejection of claims 1-5 based upon 35 U.S.C. §§ 101 and 112, first paragraph, for the following reasons. Specifically, data for PRO3566 does not appear in the table (Exhibit B). Furthermore, it is not clear how the clones appearing in the table compare to PRO3566, or if the results presented in the table were determined by the

same methodology as presented in Example 18 of the instant specification. For example, how highly expressed were the genes in Exhibit B that purportedly correlate with increased protein levels, 2-fold, 5-fold, 10-fold? How many samples were used? By what means was the level of mRNA expression determined, e.g., microarray, Northern blot, quantitative PCR? Was the "universal normal control" used or were matched tissue controls used? The declaration only states that levels of mRNA and protein in tumor tissue were compared to normal tissue.

Furthermore, all of Applicant's newly cited references, with the exception of Futcher et al., are directed to the analysis of single genes, or a small group of genes, and therefore do not demonstrate trends found across proteins in general. The studies cited by Applicant that examine the expression of specific genes or small numbers of genes are not found persuasive in view of comprehensive studies where significantly larger numbers of transcripts and proteins were examined and more accurately describe general trends, specifically, Haynes (80 proteins examined), Chen (165 proteins examined) and Nagaraja et al. (2006), Waghray et al. (2001) and Sagynaliev et al. (2006) (described below).

With regard to the Orntoft reference, Applicants submit that Orntoft examined 40 well-resolved abundant proteins, and found significant correlation between mRNA and protein alterations (including both increases and decreases) for each gene, except one. Applicants' arguments with respect to Orntoft have been fully considered but are not found to be persuasive. Orntoft et al. appear to have looked at increased DNA content over large regions of chromosomes and compare that to mRNA and polypeptide levels

from the chromosomal region. Their approach to investigating gene copy number was termed CGH. Orntoft et al. do not appear to look at gene amplification, mRNA levels and polypeptide levels from a single gene at a time. Orntoft et al. concentrated on regions of chromosomes with strong gains of chromosomal material containing clusters of genes (pg 40). This analysis was not done for PRO3566 in the instant specification. That is, it is not clear whether or not PRO3566 is in a gene cluster in a region of a chromosome that is highly amplified. Therefore, the relevance, if any of Orntoft et al. is not clear.

Applicant also asserts that Futcher et al. (1999) conducted a study of mRNA and protein expression in yeast and report a good correlation between protein abundance, mRNA abundance, and codon bias. Applicant's arguments have been fully considered but are not found to be persuasive. Futcher et al concludes that "[t]his validates the use of mRNA abundance as a rough predictor of protein abundance, at least for relatively abundant proteins [emphasis added]" (pg 7368, col 1). Futcher et al. also admits that Gygi et al. performed a similar study and generated similar data, but reached a different conclusion. Futcher et al. indicates that "Gygi et al. feel that mRNA abundance is a poor predictor of protein abundance" (pg 7367, col 1, 1st full paragraph).

The Examiner maintains the previous argument that mRNA levels are not necessarily predictive of protein levels, and in response to Applicants' arguments, maintains that this is true even when there is a change in the mRNA level. Comprehensive studies where significantly large numbers of transcripts and proteins were examined report that increases in mRNA and protein samples are not correlated.

Nagaraja et al. (Oncogene, 25:2328-2338, 2006) characterized comprehensive transcript and proteomic profiles of cell lines corresponding to normal breast (MCF10A), noninvasive breast cancer (MCF7) and invasive breast cancer (MDS-MB-231 and report that "the proteomic profiles indicated altered abundance of fewer proteins as compared to transcript profiles" (see abstract), and "the comparison of transcript profiles with proteomic profiles demonstrated that altered proteins were not always represented in the microarray designated profiles and vice versa" (see pg 2329, first column). Nagaraja et al. further report that, "a comparative analysis of transcripts and proteins to establish a relationship between transcript changes and protein levels has not yet become routine" (see pg 2328, second column). Lastly, Nagaraja et al. report that, "as dictated by post-transcriptional regulation, protein profiles showed far fewer changes as compared to transcript profiles" (see pg 2335, first column).

Similar results were reported by Waghray et al. (Proteomics, 1:1327-1338, 2001). Waghray et al. analyzed gene expression changes induced by dihydrostesterone (DHT) in the androgen responsive cancer line LNCaP, at both RNA and protein levels (see abstract). In this study, Waghray et al identified transcripts from 16750 genes and found 351 genes were significantly altered by DHT treatment and the RNA level, and identified 1031 proteins and found 44 protein spots that changed in intensity (either increased or decreased). Out of the 44 protein spots that changed in intensity, Waghray et al. reports that, "remarkably, for most of the proteins identified, there was no appreciable concordant change at the RNA level" (see pg 1333-1334, Table 4). Waghray et al. clearly state that, "The change in intensity for most of the affected

proteins identified could not be predicted based on the level of the corresponding RNA" (see abstract).

In a review of gene expression in colorectal cancer (CRC), Sagynaliev et al. (Proteomics, 5:3066-3078, 2005) report that "it is also difficult to reproduce transcriptomics results with proteomics tools. Out of 982 genes found to be differentially expressed in human CRC by genome-wide transcriptomics technologies (Table 6a), only 177 (18%) have been confirmed using proteomics technologies" (see pg 3068).

In summary, it is clear that Nagaraja, Waghray and Sagynaliev support the Examiner's position that changes in mRNA expression frequently do not result in changes in protein expression. It is also noted that the specification of the instant application does not teach a change in mRNA level of PRO3566. The specification simply discloses a static measurement of PRO3566 mRNA in melanoma and esophageal tumor as compared to normal skin and esophagus. There are no teachings in the specification as to the differential expression of PRO3566 mRNA in the progression of cancer or in response to different treatments of hormones (for example). Therefore, the Examiner maintains that Applicant's measurement of an increase of PRO3566 mRNA does not provide a specific and substantial utility for the encoded protein, or an antibody to the protein.

The state of the art, as evidenced through textbooks and review papers, clearly establishes that polypeptide levels cannot be accurately predicted from mRNA levels. Lilley et al. teach that "DNA chips (mRNA profiling studies) can contribute to the study of gene expression in response to a particular biological perturbation. However, the

extrapolation that changes in transcript level will also result in corresponding changes in protein amount or activity cannot always be made" ("Proteomics" Molecular Biology in Cellular Pathology, (2003) England: John Wiley & Sons, page 351). Wildsmith et al. also disclose that the gene expression data obtained from a microarray may differ from protein expression data ("Gene Expression Analysis Using Microarrays" Molecular Biology in Cellular Pathology, (2003) England: John Wiley & Sons, pages 269-286, especially pg 283). King et al. disclose that "it has been established that mRNA levels do not necessarily correlate with protein levels" (pg 2287, 2nd full paragraph). King et al. state that it has been demonstrated that correlation between mRNA and protein abundance is less than 0.5 and that "mRNA expression studies should be accompanied by analyses at the protein level" (pg 2287, bottom of col 1 through the top of col 2; see also Bork et al., Genome Res 398-400, 2000, especially pg 398, bottom of col 3). Haynes et al. teach that "[p]rotein expression levels are not predictable from the mRNA expression levels" (pg 1863, top of left column) and "only the direct analysis of mature protein products can reveal their correct identities, their relevant state of modification and/or association and their amounts" (pg 1870, under concluding remarks). Madoz-Gurpide et al. disclose that "[f]or most of the published studies it is unclear how well RNA levels reported correlate with protein levels" (pg 53, 1st full paragraph).

However, the specification of the instant application has only disclosed that the PRO3566 polynucleotide is differentially expressed in melanoma and esophageal tumor. The specification does not indicate that the PRO3566 polypeptide has been differentially expressed in the melanoma and esophageal tumor sample tested. Given

the asserted increase in PRO3566 expression, and the evidence provided by the current literature, it is clear that one skilled in the art would not assume that an increase in mRNA expression would correlate with significantly increased polypeptide levels. Further research needs to be done to determine whether the purported increase in PRO3566 DNA supports a role for the peptide in the cancerous tissue; such a role has not been suggested by the instant disclosure. Such further research requirements make it clear that the asserted utility is not yet in currently available form, i.e., it is not substantial. This further experimentation is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. As discussed in Brenner v. Manson, (1966, 383 U.S. 519, 148 USPQ 689), the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and,
> "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

Accordingly, the specification's assertions that the PRO3566 proteins have utility in the fields of cancer diagnostics is not substantial.

Although listed on the PTO-1449, the Examiner did not find a copy of the Stein et al. or Godbout et al. references in the application, so Applicant's arguments concerning these references could not be considered persuasive.

Additionally, although proteomics is a complementary technology to DNA measuring techniques, such as microarrays, it is quite clear that the state of the art is such that polypeptide levels cannot be accurately predicted from mRNA levels. Celis et

al. emphasize that proteins are frequently the functional molecules and, therefore, the most likely to reflect differences in gene expression (pg 6, bottom of col 1). Celis et al. continue to explain that "[g]enes may be present, they may be mutated, but they are not necessarily transcribed. Some messengers are transcribed but not translated, and the number of mRNA copies does not necessarily reflect the number of functional protein molecules" (pg 6, col 2). Madoz-Gurpide et al. teach that there is also intense interest in the scientific field in applying proteomics to disease marker identification and such approaches include comparative analysis of protein expression in normal and cancer tissues to identify aberrantly expressed proteins that may represent novel markers (pg 54, 2nd full paragraph). Wildsmith et al. also disclose that the gene expression data obtained from a microarray may differ from protein expression data ("Gene Expression Analysis Using Microarrays" Molecular Biology in Cellular Pathology, (2003) England: John Wiley & Sons, pg 283). Thus, the state of the art supports the Examiner's assertion that nucleotide levels cannot accurately predict protein levels and that analysis of protein expression is required to identify a protein as a potential marker for cancer.

Without more specifics about necessary sample size, expression level range for normal and tumor tissues, the specification has not provided the invention in a form readily usable by the skilled artisan such that significant further experimentation is unnecessary. The importance of replication in microarray gene expression studies is also demonstrated by Lee et al. (Proc. Natl. Acad., USA, 97(18):9834-9839, 2000) who report that, "our results show that any single microarray output is subject to substantial

variability" and "we recommend that at least three replicates be used in designing experiments using cDNA microarrays" (see pg 9834, second column). A single output yields numerous misclassifications, especially numerous false positives (Lee et al., bottom of pg 9838). The importance of replication in microarray gene expression studies is also important when one considers the problem of variations within "normal" gene expression levels as reported by King et al. (JAMA, 286(18):2280-2288, 2006). King et al. report that "a significant portion of microarray data variability for high- or medium-abundance mRNAs may simply be due to normal expression variations" and that "Several previous studies have used arbitrary 2-fold change criteria to define significant expression change. However, the 2-fold threshold has been shown to be statistically invalid even for duplicate experiments" (see pg 2284, first column).

It is worth noting here that the PRO3566 gene and polypeptide of the instant application have not been associated with tumor formation or the development of cancer, nor have they been shown to be predictive of such. The specification merely demonstrates that PRO3566 was purportedly differentially expressed, in opposite directions (one cancer sample up, the other down), between two cancer samples. No mutation or translocation of PRO3566 has been associated with any type of cancer versus normal tissue.

5. The rejection of claims 14-17 under 35 U.S.C. 112, first paragraph, for failing to comply with the written description requirement, is maintained for reasons of record and the following. Applicants argue that the claimed polypeptides are not defined only by sequence identity, but that they now recite specific functional limitations that the

polypeptide is more highly expressed in normal skin and esophageal tumor than in melanomas or esophagus or the polypeptides can be used to raise antibodies that recognize SEQ ID NO:64. Applicants argue that based on the high percentage of sequence identity and the described method of detecting and quantifying overexpression in tumors, one skilled in the art would have known at the time of the invention that Applicants had possession of the claimed polypeptides. Applicants' arguments have been fully considered but have not been found to be persuasive. As stated above, the claims have no functional limitations. In addition, the specification does not provide a utility or function for PRO3566. The claimed polypeptide sequences may have functions and structures which differ greatly from that of PRO3566, and therefore one of skill in the art would not be able to predictably identify the encompassed molecules as having the same functional limitations to those instantly claimed.

Applicant's arguments filed 8/17/05 have been fully considered but they are not persuasive because Applicant argues that mere sequence identity (95% or 99%) bestows upon the claimed invention all of the functional limitations recited in the instant claims. This is unpersuasive because functional limitations cannot be predicted from a protein's amino acid sequence (see Rudinger, especially page 6). Without a more adequate written description of which amino acids in the PRO3566 sequence bestow upon itself its recited functional limitations (presence in various tissues, ability to make specific antibodies to SEQ ID NO:64), these instant claims lack an adequate written description. For instance, a polypeptide sharing 95% amino acid sequence identity with

SEQ ID NO:64 would be capable of being used to make antibodies not only specific to SEQ ID NO:64, but also specific to its own sequence and a great many related sequences.

Applicant's arguments filed 2/16/06 have been fully considered but they are not persuasive because In re Wallach concerns different degenerate nucleic acids that encode an identical polypeptide, and not the situation here, where Applicant is claiming different, non-degenerate nucleic acids that encode different polypeptides.

Applicant's arguments filed 7/24/06 have been fully considered but they are not persuasive because Applicant argues that the Examiner has simply made a conclusory statement regarding the non-enablement of using a sequence 95 or 99% similar to SEQ ID NO:64 to raise antibodies that would specifically recognize SEQ ID NO:64, yet not specifically recognize yet a separate third sequence that is within the 95 or 99% similar to SEQ ID NO:64 genus, but not the exact same sequence used to raise the antibodies. The Examiner disagrees; the point has previously been raised concerning antibody binding to shared epitopes between sequences. Applicant has not rebutted why there would not be cross-reactions of antibody binding among different sequences that share 95 or 99% sequence identity.

6. Claims 6-8 and 11-17 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. Applicant states that a specific and substantial asserted utility, has been described above.

Specifically, since Applicant has not provided evidence to demonstrate that the PRO3566 polypeptide have a specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention. It is noted that the instant specification is required to teach one skilled in the art how to make and use the claimed proteins. However, there is no utility for a polypeptide comprising SEQ ID NO: 64. Uses such as assaying for binding partners (p. 95), using polypeptides as molecular weight markers (p. 92), and screening for agonists and antagonists of PRO3566 (p. 95-99) are useful only in research to determine the function of the encoded protein itself. There is no "specific benefit in currently available form" to be derived from such studies. Appellants also teach that the PRO3566 polypeptide or agonists or antagonists of PRO3566 may be used in the preparation of medicaments or in gene therapy. Even though Applicants teach that PRO3566 DNA is "more highly expressed" in normal skin cells and esophageal tumor cells when compared to melanoma tumor cells and normal esophageal cells, respectively (p. 142), there is no guidance in the specification as to how high the levels are. The asserted utility in diagnosis and treatment of the aforementioned cancers is not substantial. It is not clear whether the overexpression of PRO3566 is correlated to the overexpression of the encoded protein. The specification fails to disclose the biological significance of this putative overexpression of the protein. The specification also does not teach whether the putative overexpression is the cause or the result of the tumors, or why purportedly high levels are found in normal skin compared to melanoma (is it a tumor suppressor?), or why high levels are purportedly found in esophageal tumor compared to normal

esophagus (is it a tumor promoter?). Clearly further research and experimentation would be required to find out whether PRO3566 is useful as asserted. See *Brenner v. Manson*, noting that "'a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion." A patent is therefore not a license to experiment. Further research would be required to determine how and if PRO3566 protein and antibodies are involved in any disease.

Furthermore, the specification, were it enabling for an isolated polypeptide comprising SEQ ID N0:64, would still not reasonably provide enablement for polypeptides having at least 95% or 99% amino acid sequence identity to the polypeptide of SEQ ID NO:64 and is maintained for reasons of record and the following. Applicants argue that one skilled in the art would know how to make and use the claimed polypeptides, and Applicants have disclosed how to determine if the claimed polypeptides or encoding nucleic acids are differentially expressed in melanoma tumors or esophageal tumors compared to normal skin or normal esophagus (p. 27). Applicants' arguments have been fully considered but have not been found to be persuasive. Being differentially expressed in melanomas or esophageal tumors is not a functional limitation. Rather, it is a characteristic of an individual sequence. Even if the specification provided support for diagnosing melanomas or esophageal tumors with PR03566, the skilled artisan would not know how to use polypeptides having sequences at least 95% or 99% sequence identity to PRO3566. Such sequences are not taught to be differentially expressed in melanomas or esophageal tumors. One skilled in the art would not know how to engineer a sequence such that it is overexpressed in certain

tissues. Claims 14-17 have the limitation "wherein said isolated polypeptide or a fragment thereof can be used to generate an antibody which can be used to specifically detect the polypeptide of SEQ ID NO:64 in skin tissue or esophagus samples." Again, this is not a functional limitation.

Applicants have not specified certain regions of SEQ ID NO:64 which contain epitopes particular to an anti-PRO3566 antibody. This is merely another means for claiming a polypeptide having a percent identity to SEQ ID NO:64. One skilled in the art would not know how to make a protein at least 95% or 99% identical to SEQ ID NO:64 such that antibodies raised against the sequence would specifically recognize SEQ ID NO:64 and not other sequences 95% or 99% identical to SEQ ID NO:64.

Applicant's arguments filed 8/17/05 have been fully considered but they are not persuasive because Applicant argues that one of skill in the art would know how to make and use variants of PRO3566 within 95% or 99% sequence identity. However, Applicant fails to address the Examiner's position that no variant nucleic acid encoding even a single polypeptide variant sharing 95% or 99% sequence identity with PRO3566 has been taught by the instant specification, either in a normal tissue sample or a cancerous one. Applicant has provided no teachings or evidence that variants of PRO3566 polypeptide having 95% or 99% sequence identity are differentially expressed, or even exist, in any tissue, healthy or diseased, so the disclosure is not commensurate in scope with, and cannot enable, the claimed invention.

Applicant's arguments filed 2/16/06 have been fully considered but they are not persuasive because Applicant argues that a variant is useful to make an antibody to a

native PRO3566 epitope. However, Applicant has not provided a convincing argument that specific certain regions of SEQ ID NO:64 contain epitopes which would be particular to an anti-PRO3566 antibody. This is merely another means for claiming a polypeptide having a percent identity to SEQ ID NO:64. Also, Applicant's have not demonstrated that the PRO3566 protein is differentially expressed in any tissue type, healthy or not, in order to make it an enabled diagnostic.

Applicant's arguments filed 7/24/06 have been fully considered but they are not persuasive because Applicant argues that the Examiner has simply made a conclusory statement regarding the non-enablement of using a sequence 95 or 99% similar to SEQ ID NO:64 to raise antibodies that would specifically recognize SEQ ID NO:64, yet not specifically recognize yet a separate third sequence that is within the 95 or 99% similar to SEQ ID NO:64 genus, but not the exact same sequence used to raise the antibodies. The Examiner disagrees; the point has previously been raised concerning antibody binding to shared epitopes between sequences. Applicant has not rebutted why there would not be cross-reactions of antibody binding among different sequences that share 95 or 99% sequence identity.

7. No claim is allowed.

8. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Technical Center 1600 general number which is (571) 272-1600.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Gucker whose telephone number is (571) 272-

0883. The examiner can normally be reached on Monday to Friday from 0930 to 1800. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, can be reached at (571) 272-0867. The fax phone number for this Group is currently (571)-273-8300.

SG

Stephen Gucker

October 2, 2006

JANET L. ANDRES
SUPERVISORY PATENT EXAMINER